1,181,570

PATENT SPECIFICATION

NO DRAWINGS

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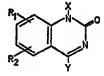
COMPLETE SPECIFICATION

Substituted Quinazolinones

We, ROUSSEL-UCLAF, a French Body Corporate of 35, Boulevard des Invalides, Paris VIIe, France, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new substituted quinazolinones and to a process for their preparation.

According to the present invention we provide quinazolinones of the general formula



(I)

(in which X is a substituted or unsubstituted alkyl group containing 1 to 6 carbon atoms, alkenyl group, or aralkyl group; the group $-CH_2Z$, wherein Z is a substituted or unsubstituted heterocyclic group or the group

$$-([CH_2]_nO)_n'-([CH_2]_mO)_m'-([CH_2]_pO)_p'-(CH_2)_qCH_3$$

wherein n, m', p' and q are 0, 1 or 2 and m and p are 1 or 2 and n' is 0 or 1.

Y is a hydrogen atom or a substituted or unsubstituted monocyclic group with aromatic character or a substituted or unsubstituted monocyclic or polycyclic cycloalkyl group; and R_1 and R_2, which may be the same or different are halogen or hydrogen atoms or substituted or unsubstituted alkyl, alkoxyl, alkylthio or alkylsulphonyl groups) wherein the alkyl moieties contain 1 to 6 carbon atoms.

Preferred compounds according to the present invention are those in which the substituent X is a methyl, ethyl, propyl, butyl, β-chloroethyl, γ-chloropropyl, carboxymethyl, methoxycarbonylmethyl, β-hydroxyethyl, γ-hydroxypropyl, β-dimethylaminoethyl, β-diethylaminoethyl, allyl, $\beta(\beta'$-ethoxy)-ethoxyethyl, benzyl or a furfuryl group; the substituent Y is a hydrogen atom or a phenyl, chlorophenyl, methoxyphenyl, ethoxyphenyl, tolyl, cyclohexyl or a pyridyl group; and the substituents R_1 and R_2 (which may be the same or different) are hydrogen atoms or chlorine, fluorine or bromine atoms or methyl, ethyl, propyl, butyl, trifluoromethyl, methoxy, ethoxy, methylthio, ethylthio, methanesulphonyl or ethanesulphonyl groups.

Particularly preferred compounds according to the present invention are:

1 - methyl - 4 - phenyl - 6 - chloro - 2-[1 *H*]-quinazolinone,
1 - methyl - 4 - ortho - tolyl - 6 - chloro-2-[1 *H*]-quinazolinone,
1 - methyl - 4 - phenyl - 6 - methoxy - 2-[1 *H*]-quinazolinone,
1 - methyl - 4 - phenyl - 7 - chloro - 2-[1 *H*]-quinazolinone,
1 - ethyl - 4 - phenyl - 6 - chloro - 2-[1 *H*]-quinazolinone,
1 - methyl - 4 - para - chloro - phenyl-6-chloro-2-[1 *H*]-quinazolinone,
1 - methyl - 4 - meta - chloro - phenyl-6-methoxy-2-[1 *H*]-quinazolinone and
1 - ethyl - 4 - ortho - tolyl - 6 - chloro-2-[1 *H*]-quinazolinone.

The compounds of general formula I according to the present invention possess noteworthy physiological properties, notably an anti-inflammatory and/or analgesic activity. They may be used for the treatment of inflammatory rheumatisms, ankylosing spondylarthritis, arthrosis and articular diseases. They are non-steroidal, strongly anti-inflammatory products and are thus free from side-effects peculiar to cortisone-type drugs and well tolerated.

They have also proved not to cause secondary effects peculiar to other non-steroidal anti-inflammatory products. Thus they do not cause headaches, gastric disorders, stomach lesions or inflammation of the intestinal mucous membrane; they do not alter the composition of the blood; they can be administered to patients suffering from kidney or heart diseases or from sensitivity phenomena due to pyrazole molecules; and they do not cause any sedation or hypnosis.

Finally they have proved to be remarkably active in human therapy, unlike many other substances which are active in animal tests but without action in human medicine.

According to a further feature of the present invention therefore, we provide pharmaceutical compositions comprising as active ingredient at least one of the compounds of the invention as herein defined in association with a pharmaceutical carrier or excipient. The compositions may be presented in a form suitable for oral, rectal, topical or parenteral administration. Thus, for example, compositions for oral administration may be solid or liquid and may take the form of granules, tablets, coated tablets, capsules, syrups, emulsions, suspensions or drops, such compositions comprising carriers or excipients conventionally used in the pharmaceutical art. Thus, for example, suitable tabletting excipients include lactose, potato and maize starches and magnesium stearate.

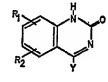
For parenteral administration, the carrier may be a sterile, parenterally acceptable liquid such as sterile water, or a parenterally acceptable oil e.g. olive oil, contained in ampoules or multi-dose flasks. Compositions for rectal administration may take the form of suppositories, the carrier comprising a suppository base.

For topical administration, on the skin or mucous membrane, the compositions can for example be formulated as ointments, creams or lotions or as topically-applied sprays or aerosols.

Advantageously, the compositions may be formulated as dosage units, each unit being adapted to supply a fixed dose of active ingredient. Tablets, coated tablets, capsules, suppositories and ampoules are examples of suitable dosage unit forms. The preferred daily dose for the adult is between 100 mg and 2.5 g and each dosage unit therefore preferably contains 50 mg to 1.0 g, and especially 100 mg to 0.5 g, of active ingredient, according to the route of administration.

Quinazolinones substituted at the 1-position were previously unknown. We have now found a route to such quinazolinones comprising treatment of the corresponding 1-*H*-quinazolinone with a basic agent followed by treatment with a reactive derivative of the desired substituent.

According to a further feature of the present invention we provide a process for the preparation of compounds of the formula I comprising reaction of a quinazolinone of the general formula



II

(in which R_1, R_2 and Y are as defined above for formula I) with a basic agent followed by reaction with a compound of the general formula

X—Q or X′—Q

(in which X is as defined for formula I; X′ is a radical convertible in the product into a radical X as defined for formula I; and Q is a reactive ester radical such as a halogen atom, a sulphate group or a substituted or unsubstituted hydrocarbon-sulphonate group e.g. an arylsulphonate group) followed by subsequent conversion of the radical X′ into X where required.

The basic agent which is reacted with the quinazolinone of formula II is preferably an alkali metal hydride, advantageously sodium hydride. Other basic agents which can be used according to the invention include, for example, sodium, sodamide, sodium ethoxide or sodium hydroxide. When an alkali metal hydride is used, it is advantageous to carry

out the reaction in dimethylformamide. This reaction may be conveniently effected at room temperature.

The reagent X—Q or X′—Q is preferably a halogenated derivative (Q=halogen). The reaction of said derivative with the quinazolinone salt is advantageously effected at room temperature.

The quinazolinones of formula II may be prepared by a process comprising condensation at an elevated temperature of an amino aldehyde or amino ketone of general formula

III

(in which R_1, R_2 and Y are as defined for formula I) with a reagent containing a N—C—O linkage, selected from the group consisting of urea, cyanic acid, a carbamate and carbamyl chloride.

If, however, the amino group in the compound of formula III is suitably substituted, a product of formula II may be obtained, and according to a still further feature of the present invention we provide a process for the preparation of compounds of the formula I comprising condensation at an elevated temperature of an amino aldehyde or aminoketone of the general formula

IV

or

IVa

(in which R_1, R_2, Y and X are as defined for formula I and X′ is a radical convertible into the radical X) with a reagent containing the linkage N—C—O, selected from urea, cyanic acid, a carbamate and carbamyl chloride, followed by subsequent conversion of the radical X′ into X where required.

Where the N—C—O compound is a carbamate it may advantageously be an alkyl carbamate.

Particularly preferred reagents containing the linkage N—C—O are urea and cyanic acid. The latter may be formed *in situ* by using an alkali metal cyanate, preferably potassium cyanate, and operating in an acid medium at a temperature of from 50° C to 60° C.

Condensation of the amino aldehyde or amino ketone, III, IV or IVa, with urea is preferably effected by admixture with urea and heating. A temperature of about 200° C and a time of heating of fifteen to thirty minutes are preferred for the condensation.

Most of the amino aldehydes or amino ketones III, IV or IVa are known compounds. The preparation of compounds III, IV and IVa, which are new, or which have been prepared by a method differing from that employed in the literature, is given below.

The following examples illustrate the invention without limiting it.

PREPARATION I:
2-amino-5-methoxy-3′-chlorobenzophenone.

Step A:
2-acetamido-5-methoxy-3′-chlorobenzophenone.

An ethereal solution of *m*-chlorophenyl magnesium bromide is prepared in the following way. To 1.45 g of pickled magnesium, covered with 10 cm3 of ethyl ether, there is added under inert atmosphere a solution of 6.95 cm3 of *m*-chlorobromobenzene in 10 cm3 of ethyl ether. After thirty minutes reflux, the reaction is complete.

Meanwhile there are dissolved under an inert atmosphere 9.05 g of 2-methyl-6-methoxy-3,1-benzoxazin-4-one (product prepared by the process of Morrisson and Mulholland J. Chem. Soc., 2702 (1958)) in a mixture of 100 cm3 of benzene and 40 cm3 of anhydrous ether. Then the ethereal solution of *m*-chlorophenyl magnesium bromide, already prepared, is introduced at 0° C and the reaction mixture is left for fifteen hours at room temperature. First ice and then dilute hydrochloric acid are added, the organic phase is separated by decantation, washed with dilute hydrochloric acid, then with water, and concentrated to dryness under reduced pressure. There are thus obtained 16.3 g of crude 2 - acetamido - 5 - methoxy - 3′ - chlorobenzophenone, used as such for the following step.

Step B:
2-amino-5-methoxy-3′-chlorobenzophenone.

Into a mixture of 100 cm3 of methanol and 35 cm3 of hydrochloric acid (22° Be = 35.2% HCl) there are introduced the 16.3 g of crude 2 - acetamido - 5 - methoxy - 3′-chloro-benzophenone obtained above, the reaction mixture is brought to reflux, and reflux is maintained for three hours. It is allowed to cool, the methanol is removed by concentration under reduced pressure and

water is added. The mixture is extracted with ethyl ether, the ethereal extracts are collected, washed with water, then with a solution of sodium bicarbonate and finally with water. The ethereal solution is concentrated to dryness under reduced pressure. The crude product thus obtained is purified in the form of the picrate. For this purpose the crude product is dissolved in boiling ethanol, 10.8 g of picric acid are added to this solution, it is allowed to cool, the precipitate formed is suction-filtered, washed, dried, and 12 g of 2 - amino - 5 - methoxy - 3' - chlorobenzophenone picrate, m.p. = 164° C are obtained.

Analysis: $C_{26}H_{17}ClN_4O_9$ = 490.81

Calculated:	C%	48.9	H%	3.1	Cl%	7.2	N% 11.4
Found :		49.5		3.2		7.2	11.3

All the picrate obtained is mixed with an aqueous solution of lithium hydroxide in presence of ethyl ether and the mixture agitated. The ethereal phase is separated by decantation, washed with water, dried, decolorised with animal charcoal, then concentrated to dryness under reduced pressure. In this way, 6.2 g of 2-amino-5-methoxy-3'-chloro-benzophenone are obtained.

A sample of this product is crystallised from methanol, m.p. = 86° C.

Analysis: $C_{15}H_{11}ClNO_2$ = 261.71

Calculated:	C%	64.25	H%	4.62	Cl%	13.55	N% 5.35
Found :		64.2		4.7		13.5	5.3

PREPARATION II:

2-amino-3-methyl-5-chloro-benzophenone.

70.75 g of 2-methyl-4-chloroaniline are slowly added to 158 g of benzoyl chloride, heated to 120° C. The N-(2'-methyl-4'-chlorophenyl) benzamide formed is not isolated. The reaction medium is then heated to 180° C, 87 g of zinc chloride are added over twenty minutes, the temperature of the reaction medium is brought to 220° C and this temperature is maintained for two hours. The reaction mixture containing the 2-benzamido - 3 - methyl - 5 - chloro - benzophenone is cooled to 120° C. 3N Hydrochloric acid is added, and the mixture is heated under reflux and the water phase is decanted off (this water phase contains benzoic acid and starting amine). This operation is repeated many times in succession. Aqueous sulphuric acid (75% by volume) is added to the organic residue, and the mixture refluxed for forty-five minutes. The solution obtained is poured on a mixture of water and ice and extracted with methylene chloride. The methylene chloride extracts are combined, washed with hydrochloric acid, then with sodium hydroxide solution, and finally with water.

The organic phase is dried, decolorised by the addition of animal charcoal, filtered and the solvent is distilled off. The residue is crystallised from methanol and 2-amino-3-methyl-5-chloro-benzophenone, m.p. = 88° C is obtained. By concentration of the methanolic mother liquors a second yield of same quality is obtained.

This product is identical to that obtained in another way in U.S. Patent No. 3,136,815.

PREPARATION III:

2-amino-5-methanesulphonyl-benzophenone.

In 40 cm3 of acetic acid, 8 g of 2-amino-5-methylthio-benzophenone are dissolved (product obtained by application of the process described in Chem. Abs. 61, 5 671), 3.7 cm3 of aqueous hydrogen peroxide (30% by weight) are added and the whole stirred for seventeen hours at room temperature, then for twenty hours at 55° C. There are then further added 1.85 cm3 of aqueous hydrogen peroxide (30% by weight and the mixture stirred for four hours at 55° C. The reaction medium is diluted with water, the precipitate formed is suction filtered, washed and dried. This crude product is crystallised from methanol and 5.3 g of 2-amino-5-methanesulphonyl-benzophenone, m.p. = 152—153° C, are obtained.

This product has been obtained by another way in U.S. patent No. 3,121,103.

EXAMPLE I:

1 - methyl - 4 - phenyl - 6 - chloro - 2-[1*H*] quinazolinone, (I with X = methyl Y = phenyl, R_3 = 6-chloro, R_2 = H).

Step A:

4-phenyl-6-chloro-2-[1*H*] quinazolinone.

a) *By condensation with potassium cyanate in acetic medium.*

11.6 g of 2-amino-5-chloro-benzophenone (obtained according to the process described by Dippy and Moss, J. Chem. Soc. 2,205—2,210 (1952)) and 4.4 g of potassium cyanate are introduced in 58 cm3 of acetic acid. The solution is heated to 55° C for fifteen hours and poured into water. The precipitate is suction filtered, washed with water, then with

ether and dried; 7.5 g of crude product are obtained. By extraction of the mother liquors with methylene chloride, then concentration to dryness, there are further obtained 1.5 g of the crude product. The 9 g obtained as a whole are crystallised from butanol; 7.2 g of 4 - phenyl - 6 - chloro - 2 - [1*H*] quinazolinone are obtained, which melt at 318° C; this product occurs in the form of prisms, which are fairly soluble in acetone, slightly soluble in alcohol, benzene and chloroform, and insoluble in water and ether.

U.V. spectrum (ethanol)

Max. at	233 mμ	(ε = 40,700)
Infl. at about	265 mμ	(ε = 9,250)
Max. at	365 mμ	(ε = 4,650)

This product is identical to that obtained in another way by Sulkowski and Childress, J. Org. Chem., *27*, 4424 (1962), m.p. = 312° C.

b) *By condensation with urea.*

80 g of 2-amino-5-chloro-benzophenone and 20 g of urea are mixed. This mixture is brought to 195° C and this temperature is kept for twenty-five minutes. The reaction mixture is then cooled, empasted with petroleum ether (b.p. = 60 to 80° C), and the product obtained is crystallised from butanol. 44 g of 4-phenyl-6-chloro-2-[1*H*] quinazolinone, m.p. = 318° C, are collected, identical to the product obtained paragraph (a), step A, Example I.

Step B:

1 - methyl - 4 - phenyl - 6 - chloro - 2-[1*H*] quinazolinone.

7.50 g of a 50% suspension of sodium hydride in mineral oil are introduced into 570 cm3 of dimethylformamide, a suspension of 40 g of 4-phenyl-6-chloro-2-[1*H*] quinazolinone, in 915 cm3 of dimethylformamide is slowly added while maintaining the temperature at 20—25° C, and the resulting mixture is stirred for thirty minutes. A solution of 20 cm3 of methyl iodide in 100 cm3 of dimethylformamide is added and the mixture is allowed to stand sixty hours at room temperature. The solution is evaporated to dryness under vacuum and water is added. The precipitate is suction filtered, washed with water, then with ether and recrystallised from ethanol: 27 g of 1-methyl-4-phenyl-6-chloro-2-[1*H*] quinazolinone, melting at 220° C are obtained.

Analysis: $C_{15}H_{11}ClN_2O$ = 270.72

Calculated:	C% 66.54	H% 4.09	Cl% 13.10	N% 10.35
Found :	66.6	4.1	13.4	10.1

U.V. Spectrum (ethanol)

Max. at	234 mμ	(ε = 46,100)
Infl. at about	267 mμ	(ε = 8,600)
Max. at	368 mμ	(ε = 5,120)

As far as it is known, this compound is not described in the literature.

EXAMPLE II:

1-methyl-4-phenyl-6-chloro-2-[1 *H*] quinazolinone.

The 1 - methyl - 4 - phenyl - 6 - chloro-[1 *H*] quinazolinone can be obtained according to following variant:

10 g of 2-methylamino-5-chlorobenzophenone (obtained according to the process described by Bell, Sulkowski et al, J. Org. Chem. *27*, 556, (1962) and 3.6 g of potassium cyanate are introduced into 100 cm3 of acetic acid. The mixture is held at 55° C for sixteen hours, cooled and poured into iced water. The precipitate is suction filtered, washed with ether and crystallised from ethanol. 5 g of 1 - methyl - 4 - phenyl - 6 - chloro - 2-[1 *H*] quinazolinone are obtained, identical to the product obtained in step B, Example I.

Analysis: $C_{16}H_{13}ClN_2O$ = 346.81

Calculated:	C% 72.72	H% 4.36	Cl% 10.22	N% 8.08
Found :	72.7	4.5	10.3	8.3

EXAMPLE III:

1 - benzyl - 4 - phenyl - 6 - chloro - 2-[1 *H*] quinazolinone, (I with X = benzyl, Y = phenyl, R_1 = 6-chloro, R_2 = H).

5 g of 4-phenyl-6-chloro-2-[1 *H*] quinazolinone, then 1 g of a 50% suspension of sodium hydride in mineral oil are introduced into 100 cm3 of dimethylformamide. The mixture is stirred for three hours at room temperature during which time 450 cm3 of hydrogen are evolved. 2.8 cm3 of benzyl bromide are then added to the suspension, which is then stirred for eighteen hours at room temperature. The dimethylformamide is distilled off under reduced pressure, water is added and the precipitate formed is suction filtered, washed and dried. This product is triturated with warm toluene and the insoluble matter is filtered off. The toluene is evaporated under reduced pressure, the residue is empasted in isopropyl ether, and crystallised from toluene. In this way 3.86 g of 1 - benzyl - 4 - phenyl - 6 - chloro - 2-[1 *H*] quinazolinone, m.p. = 182° C are obtained.

As far as it is known, this compound is not described in the literature.

EXAMPLE IV:

1 - (β - diethylaminoethyl) - 4 - phenyl - 6-chloro-2-[1 *H*] quinazolinone, (I with X = β-diethyl amino ethyl, Y = phenyl, R_1 = 6-chloro, R_2 = H).

0.685 g of a 55% suspension of sodium hydride in mineral oil are introduced into 50 cm3 of dimethylformamide and a suspension of 4 g of 4-phenyl-6-chloro-2-[1 *H*] quinazolinone in 50 cm3 of dimethylformamide is added at room temperature over about one hour.

A total of 350 cm3 of hydrogen is collected. A solution of 4 g of β-diethylaminoethyl chloride in 20 cm3 of ethyl ether is introduced and it is stirred for fifteen hours at room temperature. The mixture is concentrated to dryness under reduced pressure, hydrochloric acid is added to the residue, the insoluble matter is filtered, the filtrate is decolorised with animal charcoal, the pH of this filtrate is brought to 8.5—9 by addition of aqueous sodium bicarbonate, the aqueous phase is extracted with ether, the ethereal extracts are combined, the solution obtained is dried and concentrated to dryness under reduced pressure. The residue is empasted in isopropyl ether, then crystallised from petroleum ether (b.p. = 65—75° C). In this way, 2.1 g of 1-(β-diethylaminoethyl)-4-phenyl-6-chloro 2[1 *H*] quinazolinone, m.p. = 100—101° C are obtained.

Analysis: $C_{20}H_{23}ClN_3O = 355.86$

	C%	H%	Cl%	N%
Calculated:	67.49	6.23	9.96	11.81
Found :	67.6	6.2	10.2	11.5

As far as it is known, this compound is not described in the literature.

EXAMPLE V:

1 - methoxy carbonyl methyl - 4 - phenyl-6-chloro-2-[1 *H*] quinazolinone, (I with X = methoxy carbonyl methyl, Y = phenyl, R_1 = 6-chloro, R_2 = H).

7.5 g of 4-phenyl-6-chloro-2-[1 *H*] quinazolinone are introduced into 200 cm3 of dimethylformamide, 1.47 g of 50% suspension of sodium hydride in mineral oil are added and the mixture is stirred for three hours at room temperature and 675 cm3 hydrogen are collected. 3 cm3 of methyl-bromoacetate are added, it is stirred for fifteen hours at room temperature, then concentrated to dryness under reduced pressure.

The residue is dissolved in methylene chloride, the organic solution obtained is washed successively with water, with aqueous sodium bicarbonate, water, dilute hydrochloric acid, and finally water. The methylene chloride solution is dried and concentrated to dryness under reduced pressure. The product obtained is chromatographed on alumina, fixation and elution being effected by means of methylene chloride.

From the least mobile fractions, 3.46 g of 1 - methoxy - carbonylmethyl - 4 - phenyl-6-chloro-2-[1 *H*] quinazolinone are obtained after crystallisation from methanol; m.p. = 167° C.

Analysis: $C_{17}H_{13}ClN_2O_3 = 328.75$

	C%	H%	Cl%	N%
Calculated:	62.11	3.99	10.78	8.52
Found :	61.9	4.3	10.8	8.2

As far as it is known, this compound is not described in the literature.

EXAMPLE VI:

1 - carboxymethyl - 4 - phenyl - 6 - chloro 2-[1 *H*] quinazolinone.

2.8 g of 1-methoxy carbonyl methyl-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone (Example V) are introduced into a mixture of 100 cm3 of methanol and 10 cm3 of 2N sodium hydroxide. The reaction mixture is refluxed. Methanol is slowly distilled for about one hour, while replacing progressively the distilled methanol by water. The solution obtained is decolorised with animal charcoal, then mixed with dilute hydrochloric acid. The precipitate formed is suction filtered, washed and dried under reduced pressure. In this way there are obtained 2.2 g of 1 - carboxymethyl - 4 - phenyl - 6-chloro-2-[1 *H*]-quinazolinone, containing water of crystallisation. By drying at 150° C the anhydrous product is obtained; m.p. = 255—260° C (with decomposition).

Analysis: $C_{17}H_{11}ClN_2O_3 = 314.73$

	C%	H%	Cl%	N%
Calculated:	61.05	3.52	11.27	8.91
Found :	60.7	3.8	11.5	8.6

As far as it is known, this compound is not described in the literature.

EXAMPLE VII:

1 - methyl - 4 - *m* - chlorophenyl - 6-methoxy - 2 - [1 *H*] - quinazolinone (R_1 = 6-methoxy, R_2 = H).

Step A:

4-*m*-chlorophenyl-6-methoxy-2-[1 *H*]-quinazolinone.

Into 40 cm³ of acetic acid there are introduced 4 g of 2-amino-5-methoxy-3'-chloro-benzophenone (Preparation I), then 1.55 g of potassium cyanate, and the mixture is stirred for fifteen hours at 58° C. 1.55 g of potassium cyanate is then added and the mixture is stirred for three hours at 58° C. Water is added, and the precipitate formed is suction filtered, dried and 4.32 g of 4-*m*-chlorophenyl - 6 - methoxy - 2 - [1 *H*]-quinazolinone, m.p. = 228° C, are obtained.

Analysis: $C_{15}H_{11}ClN_2O_2 = 286.5$

Calculated:	C%	62.83	H%	3.87	N%	9.77	Cl%	12.37
Found :		62.9		3.9		9.5		12.2

Step B:

1 - methyl - 4 - *m* - chlorophenyl - 6-methoxy-2-[1 *H*]-quinazolinone.

Into 100 cm3 of dimethylformamide there are introduced 4 g of 4-*m*-chlorophenyl-6-methoxy-2-[1 *H*]-quinazolinone, then 0.74 g of 50% suspension of sodium hydride in mineral oil. The mixture is stirred for three hours and 305 cm3 of hydrogen are collected. 1.15 cm3 of methyl iodide in solution in 5 cm3 of dimethylformamide are added, the mixture is stirred for two hours and the dimethylformamide is removed under reduced pressure. Water is added and the mixture is stirred, the aqueous phase is extracted with methylene chloride, the methylene chloride extracts are combined and the organic solution obtained is washed with water, dried and concentrated to dryness under reduced pressure. The residue is crystallised from toluene, and in this way 1.89 g of 2-methyl-4-*m*-chlorophenyl - 6 - methoxy - 2 - [1 *H*]-quinazolinone, m.p. = 199° C are obtained.

Analysis: $C_{16}H_{13}ClN_2O_2 = 300.5$

Calculated:	C%	63.90	H%	4.36	Cl%	11.79	N%	9.32
Found :		64.2		4.4		11.8		9.0

As far as it is known, this compound is not described in the literature.

EXAMPLE VIII:

1 - methyl - 4 - phenyl - 7 - chloro - 2 - [1 *H*]-quinazolinone (I with X = methyl, Y = phenyl, R_1 = 7-chloro, R_2 = H).

Step A:

4-phenyl-7-chloro-2-[1 *H*]-quinazolinone.

15 g of 2-amino-4-chloro-benzophenone (product prepared by application of the process L. H. Sternbach, J. Org. Chem. *27*, 3781, (1962)) are mixed with 3.9 g of urea and the vessel containing this mixture is dipped into a metal bath at 220° C. After forty minutes heating, the reaction medium is brought to room temperature, the solid formed is empasted in hot ethanol and there are obtained 8 g of crude 4-phenyl-7-chloro-2-[1 *H*]-quinazolinone, m.p. = 286—287° C, used as such for the following step.

Analysis: $C_{14}H_9N_2OCl = 256.69$

Calculated:	C%	65.50	H%	3.53	N%	10.92	Cl%	13.81
Found :		65.8		3.6		10.9		13.5

Step B:

1-methyl-4-phenyl-7-chloro-2-[1 *H*]-quinazolinone.

1.31 g of 50% suspension of sodium hydride in mineral oil is introduced into 26 cm3 of dimethylformamide, then there is added over one hour, at room temperature, a solution of 7 g of 4-phenyl-7-chloro-2-[1 *H*]-quinazolinone in 100 cm3 of dimethylformamide. The mixture is stirred for one hour at room temperature, then for two hours thirty minutes at 50° C and 720 cm3 of hydrogen are collected. It is allowed to cool at room temperature, then a solution of 4.65 g of methyl iodide in 8 cm3 of dimethylformamide is introduced over thirty minutes. The reaction mixture is left for fifteen hours at room temperature, then concentrated to dryness under reduced pressure, the residue is dissolved in methylene chloride and the methylene chloride solution is washed with water, dried and concentrated to dryness

under reduced pressure. The residue is crystallised from ethanol and in this way 4.8 g of 1 - methyl - 4 - phenyl - 7 - chloro-2-[1 *H*]-quinazolinone, m.p. = 190° C are obtained.

Analysis: $C_{16}H_{11}N_3OCl = 270.72$

Calculated:	C%	66.54	H%	4.09	N%	10.35	Cl% 13.10
Found :		66.5		4.4		10.2	13.0

As far as it is known, this compound is not described in the literature.

In a similar way, starting from the 4-phenyl - 6 - chloro - 2 - [1 *H*] - quinazolinone, the compounds I are obtained, the preparation and characteristics of which are indicated in Table A.

In the column headed "Analysis" the upper numbers are the calculated percentages and the lower numbers are the percentages determined experimentally.

As far as it is known, the N-substituted quinazolinones in Table A are not described in the literature.

TABLE A

Reagent condensed with 4-phenyl-6-chloro-2-[1 *H*]-quinazolinone	Name of the quinazolinone obtained	Substituents of quinazolinone of formula I				Melting Point	Analysis			
		X	Y	R_1	R_2		C%	H%	N%	Cl%
ethyl iodide	1-ethyl-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone	ethyl	phenyl	6-chloro	H	168°C	67.49 67.6	4.60 4.8	9.84 9.5	12.45 12.5
n-butyl bromide	1-n-butyl-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone	n-butyl	phenyl	6-chloro	H	205°C	69.11 69.05	5.47 5.4	8.95 9.0	11.33 11.5
allyl bromide	1-allyl-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone	allyl	phenyl	6-chloro	H	190°C	68.80 68.6	4.41 4.6	9.44 9.0	11.94 11.8
2-bromoethanol	1-β-hydroxyethyl-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone	β-hydroxyethyl	phenyl	6-chloro	H	200°C	63.9 64.1	4.35 4.4	9.31 9.0	11.79 11.7
3-chloropropan-1-ol	1-γ-hydroxypropyl-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone	γ-hydroxypropyl	phenyl	6-chloro	H	136°C	64.86 65.2	4.80 4.9	8.90 8.7	11.26 11.4
1-chloro-2-[β'-(β-ethoxy)-ethoxy]-ethane	1-[β-(β'-ethoxy)-ethoxyethyl]-4-phenyl-6-chloro-2-[1 H]-quinazolinone	β-(β'-ethoxy)-ethoxyethyl	phenyl	6-chloro	H	70°C	64.42 64.2	5.68 5.9	9.51 9.2	7.51 7.3
furfuryl bromide	1-furfuryl-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone	furfuryl	phenyl	6-chloro	H	200°C	67.75 68.1	3.88 4.2	8.32 8.6	10.52 10.6

EXAMPLE IX:

1 - (γ - chloropropyl) - 4 - phenyl - 6-chloro - 2 - [1 *H*] - quinazolinone (I with X = γ-chloropropyl, Y = phenyl, R_1 = 6-chloro, R_2 = H).

2.1 g of 1-(γ-hydroxypropyl)-4-phenyl-6-chloro-2-[1 *H*]-quinazolinone (Table A) are introduced into a mixture of 14 cm3 of chloroform and 1.4 cm3 of dimethylaniline, the mixture is cooled to − 5° C and a solution of 0.77 cm3 of thionyl chloride in 10 cm3 of chloroform is introduced. The mixture is stirred for fifteen minutes at 0° C, then refluxed for forty-five minutes. The reaction mixture is allowed to cool, poured into dilute hydrochloric acid, the aqueous phase is extracted with chloroform, the chloroform extracts are combined and successively washed with dilute hydrochloric acid, with water, with aqueous sodium bicarbonate and finally with water. The chloroform solution is dried, then concentrated to dryness under reduced pressure. The residue is purified by crystallisation from acetone and 1.29 g of 1-(γ-chloropropyl) - 4 - phenyl - 6 - chloro - 2 - [1 *H*]-quinazolinone, m.p. = 152° C, then 170° C are obtained.

Analysis: $C_{17}H_{14}N_2OCl_2 = 333.21$.

Calculated:	C% 61.27	H% 4.23	N% 8.40	Cl% 21.28
Found :	61.3	4.3	8.4	21.4

As far as it is known, this product is not described in the literature.

EXAMPLE X:

1 - ethyl - 4 - *o* - tolyl - 6 - chloro - 2-[1 *H*]-quinazolinone (I with X = CH_2CH_3, Y = *o*-tolyl, R_1 = Cl in position 6, R_2 = H).

Step A:

4-*o*-tolyl-6-chloro-2-[1 *H*]-quinazolinone.

9.4 g of 2-amino-5-chloro-2'-methyl-benzophenone and 3.84 g of potassium cyanate are introduced into 95 cm3 of acetic acid, stirred and heated to 56° C for 16 hours; the solution obtained is poured into a water-ice mixture, suction filtered and the filter-cake washed with water and dried under vacuum at 75° C; the residue is dissolved in 300 cm3 of methanol under reflux, treated with animal charcoal, filtered warm and 230 cm3 of solvent are distilled off; it is then ice cooled for one hour, suction filtered, washed with ice cooled methanol and dried under vacuum at 75° C; 4.87 g of crude product, m.p. 263° C are collected. By concentration of the methanol mother liquors, a second yield of 0.735 g, is collected, that is a total yield of 54%. For analysis, the 4-*o*-tolyl-6-chloro-2-[1 *H*]-quinazolinone is purified by recrystallisation from toluene.

The product appears as colourless prisms, which are soluble in alcohol, acetone and chloroform, slightly soluble in ether and benzene and insoluble in water; m.p. = 267—268° C.

Analysis: $C_{15}H_{11}ClN_2O = 270.6$

Calculated:	C% 66.54	H% 4.10	N% 10.35	Cl% 13.10
Found :	66.3	4.3	10.5	12.9

The starting product, the 2-amino-5-chloro-2'-methyl-benzophenone can be obtained according to the process described by Sternbach, J. Org. Chem., *27*, 3781 (1962).

Step B:

1-ethyl-4-*o*-tolyl-6-chloro-2-[1 *H*]-quinazolinone.

3.63 g of 4-*o*-tolyl-6-chloro-2-[1 *H*]-quinazolinone are dissolved in 80 cm3 of dimethylformamide, 680 mg of a 50% suspension of sodium hydride in oil are added, and the mixture is stirred for twenty minutes, and 310 cm3 of hydrogen are collected, 2.73 g of ethyl iodide are added, the mixture is stirred for three hours then a further 1.9 g ethyl iodide are introduced and the mixture is stirred for 19 hours 30 minutes; it is distilled to dryness under vacuum, ice is added to the residue, which is then suction filtered, washed with water and dried under vacuum. The residue is empasted with petroleum ether and dried, then dissolved in 25 cm3 of ethyl acetate with reflux, treated with animal charcoal, filtered warm, ice-cooled for 1 hour, washed with ice-cooled ethyl acetate and dried under vacuum. 1.83 g of the crude-ethyl product is collected, which is purified by recrystallisation from ethyl acetate; 1.44 g of 1-ethyl-4-*o*-tolyl-6-chloro-2-[1 *H*]-quinazolinone (yield 36%) melting at 174—175° C are obtained.

The 1 - ethyl - 4 - *o* - tolyl - 6 - chloro-2-[1 *H*]-quinazolinone appears as light yellow needles, which are soluble in most common organic solvents, slightly soluble in ether and insoluble in water.

Analysis: $C_{17}H_{15}ClN_2O = 298.77$

Calculated:	C%	68.34	H%	5.06	Cl%	11.87	N%	9.38
Found :		68.3		5.1		12.0		9.2

As far as it is known, this compound is not described in the literature.

In the same way, by starting from different aminoketones, there are obtained in a similar manner to that described above the corresponding intermediate N_1-*H*-quinazolinones, II, the preparations and characteristics of which are summarized in Table B.

In the 2nd column, Table B, the letter C indicates that the aminoketone, III is condensed with a cyanate in an acetic acid medium, and the letter U, that the aminoketone, III, is condensed with urea. The reagent for the introduction of the substituent X in the N_1-X quinazolinones obtained is, in all cases, methyl iodide.

The N_1-X-quinazolinones, which are in Table B, are not, so far as is known, described in the literature.

TABLE B

Starting aminoketone and process for its preparation	Condensation agent	N_1—H—quinazolinones obtained: Substituents and names			Melting point	N_1—X—quinazolinones obtained: Substituents and names				Melting point
		Y	R_1	R_2		X	Y	R_1	R_2	
2-amino-5-methoxy-benzophenone (Sternbach, J. Org. Chem. *27*, 3781 (1962))	C	phenyl	6-methoxy	H	287°C	methyl	phenyl	6-methoxy	H	166°C
		4-phenyl 6-methoxy-2-[1*H*]-quinazolinone				1-methyl-4-phenyl-6-methoxy-2-[1*H*]-quinazolinone				
2-amino-benzophenone (Beilstein *14*, 76)	C	phenyl	H	H	251—252°C	methyl	phenyl	H	H	136—137–C
		4-phenyl-2-[1*H*]-quinazolinone				1-methyl-4-phenyl-2-[1*H*]-quinazolinone				
2-amino-5-chloro-4'-methoxy benzophenone (Davis and Pizzini, J. Org. Chem. *25*, 1884 (1960))	U	p-methoxy-phenyl	6-chloro	H	306°C	methyl	*p*-methoxy-phenyl	6-chloro	H	216°C
		4-p-methoxyphenyl-6-chloro-2-([1*H*]-quinazolinone				1-methyl-4-*p*-methoxyphenyl-6-chloro-2-[1*H*]-quinazolinone				
2-amino-5-trifluoromethyl-benzophenone (Maxwell, Garden et al., Arzneimittel Forsch. *13*, 802, 1963)	U	phenyl	6-trifluoro-methyl	H	229°C	methyl	phenyl	6-trifluoro-methyl	H	198°C 200°C
		4-pheny-6-trifluoromethyl-2-[1*H*]-quinazolinone				1-methyl-4-phenyl-6-trifluoromethyl-2-[1*H*]-quinazolinone				
2-amino-5-methylthio-benzophenone (C.A., *61*, 5671)	C	phenyl	6-methylthio	H	250°C	methyl	phenyl	6-methylthio	H	158°C
		4-phenyl-6-methylthio-2-[1*H*]-quinazolinone				1-methyl-4-phenyl-6-methylthio-2-[1*H*]-quinazolinone				

TABLE B (Continued)

Starting aminoketone and process for its preparation	Condensation agent	N_1—H—quinazolinones obtained: Substituents and names			Melting point	N_1—X—quinazolinones obtained: Substituents and names				Melting point
		Y	R_1	R_2		X	Y	R_1	R_2	
2-amino-5-methanesulphonyl-benzophenone (Preparation III)	C or U	phenyl	6-methane sulphonyl	H	378 °C	methyl	phenyl	6-methane sulphonyl	H	238 °C
		4-phenyl 6-methanesulphonyl-2-[1*H*]-quinazolinone				1-methyl-4-phenyl-6-methanesulphonyl-2-[1*H*]-quinazolinone				
2-amino-3,5-dichloro-benzophenone (Sternbach, J.Org.Chem. *26*, 4488)	C or U	phenyl	6-chloro	8-chloro	333—334 °C	methyl	phenyl	6-chloro	8-chloro	360 °C (sublimation)
		4-phenyl-6,8-dichloro-2-[1*H*]-quinazolinone				1-methyl-4-phenyl-6,8-dichloro 2-[1*H*]-quinazolinone				
2-amino-3-methyl-5-chloro-benzophenone (Preparation II)	C	phenyl	6-chloro	8-methyl	346 °C	methyl	phenyl	6-chloro-	8-methyl	325 327 °C
		4-phenyl 6-chloro 8-methyl-2-[1*H*]-quinazolinone				1,8-dimethyl-4-phenyl-6-chloro-2-[1*H*]-quinazolinone				
2-amino-2′,5-dichloro-benzophenone (Sternbach, J.Org.Chem., *26*, 4488)	C	ortho-chloro-phenyl	6-chloro	H	330 °C	methyl	ortho-chloro-phenyl	6-chloro	H	198 °C
		4-orthochlorophenyl-6-chloro-2-[1*H*]-quinazolinone				1-methyl-4-orthochlorophenyl-6-chloro-2-[1*H*]-quinazolinone				
2-amino-6-chlorobenzophenone (Sternbach et al. J. Org. Chem., *27*, 3781—3788 (1962))	C	phenyl	5-chloro	H	284 °C	methyl	phenyl	5-chloro	H	259 °C
		4-phenyl-5-chloro-2-([1*H*]-quinazolinone				1-methyl-4-phenyl-5-chloro-2-[1*H*]-quinazolinone				

TABLE B (Continued)

Starting aminoketone and process for its preparation	Condensation agent	N_1—H—quinazolinones obtained: Substituents and names			Melting point	N_1—X—quinazolinones obtained: Substituents and names				Melting point
		Y	R_1	R_2		X	Y	R_1	R_2	
2-amino-4',5-dichloro-benzophenone (Sternbach, J.Org.Chem., *26*, 4488)	C	para-chloro-phenyl	6-chloro	H	276°C	methyl	parachloro-phenyl	6-chloro	H	222°C
		4-parachlorophenyl-6-chloro-2-[1*H*]-quinazolinone				1-methyl-4-parachlorophenyl-6-chloro-2-[1*H*]-quinazolinone				
2-amino-5-chloro-2'-methyl-benzophenone (Sternbach et al. J. Org. Chem., *27*, 3781, 1962)	C	ortho-tolyl	6-chloro	H	267 268°C	methyl	ortholyl	6-chloro	H	212-213°C
		4-orthotolyl-6-chloro-2-[1*H*]-quinazolinone				1-methyl-4-orthotolyl-6-chloro-2-[1*H*]-quinazolinone				
2-amino-5-chlorophenyl-cyclohexyl-ketone Bull et al.J.Med.Pharm.Chem. *5*, 63, 1962)	U	cyclo-hexyl	6-chloro	H	275—277°C	methyl	cyclohexyl	6-chloro	H	171—172°C
		4-cyclohexyl-6-chloro-2-[1*H*]-quinazolinone				1-methyl-4-cyclohexyl-6-chloro-2-[1*H*]-quinazolinone				

The following quinazolinones of general formula I are obtained in a similar manner to that described above:

1 - methyl - 6 - chloro - 2 - [1 *H*]-quinazolinone (m.p. >280° C);

1 - methyl - 2 - [1 *H*] - quinazolinone (m.p. = 142°±2° C, then about 260° C);

1 - methyl - 4 - phenyl - 6 - [(β - (β'-ethoxy) - ethoxy - ethoxy] - 2 - [1 *H*]-quinazolinone (m.p. about 75° C);

1 - methyl - 4 - *p* - cyclohexylphenyl - 6-chloro-2-[1 *H*]-quinazolinone (m.p. = 230° C);

1 - methyl - 4 - phenyl - 6 - fluoro - 2-[1 *H*]-quinazolinone (m.p. = 188° C);

1 - methyl - 4 - (4' - pyridyl) - 6 - chloro-2[1 *H*]-quinazolinone (m.p. = 268° C);

1 - methyl - 4 - phenyl - 6,7 - dichloro-2[1 *H*]-quinazolinone;

1 - methyl - 4 - *o* - isopropylphenyl - 6-chloro-2-[1 *H*]-quinazolinone;

1 - methyl - 4 - *p* - methanesulphonyl-phenyl - 6 - chloro - 2[1 *H*] - quinazolinone;

1 - methyl - 4 - *p* - methylthiophenyl - 6-chloro-2[1 *H*]-quinazolinone;

1 - methyl - 4 - *o* - carboxyphenyl - 6-chloro-2-[1 *H*]-quinazolinone;

1 - methyl - 4 - *o,o'* - dimethylphenyl - 6-chloro-2-[1 *H*]-quinazolinone;

1 - methyl - 4 - *o* - methoxycarbonylphenyl-6-chloro-2-[1 *H*]-quinazolinone;

1 - methyl - 4 - phenyl - 6 - bromo - 2-[1 *H*]-quinazolinone;

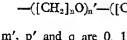
1 - methyl - 4 - *p* - fluorophenyl - 6-chloro-2-[1 *H*]-quinazolinone;

1 - methyl - 4 - *m* - chlorophenyl - 6-chloro-2-[1 *H*]-quinazolinone;

1 - methyl - 4 - *o* - fluorophenyl - 6-chloro-2-[1 *H*]-quinazolinone; and

1 - methyl - 4 - phenyl - 6 - methyl - 2-[1 *H*]-quinazolinone.

As far as is known, these compounds are not described in the literature.

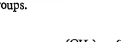


wherein n, m', p' and q are 0, 1 or 2 and m and p are 1 or 2, and n' is 0 or 1.

Y is a hydrogen atom or a substituted or unsubstituted monocyclic group with aromatic character or a substituted or unsubstituted monocyclic or polycyclic cycloalkyl group; and

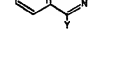
R_1 and R_2, which may be the same or different are halogen or hydrogen atoms or substituted or unsubstituted lower alkyl, alkoxyl, alkylthio or alkylsulphonyl groups wherein the alkyl moieties contain 1 to 6 carbon atoms).

2. Compounds as claimed in Claim 1 in which the substituent X is a methyl, ethyl, propyl, butyl, β-chloroethyl, γ-chloropropyl, carboxymethyl, methoxycarbonylmethyl, β-hydroxyethyl, γ-hydroxypropyl, β-dimethylaminoethyl, β-diethylaminoethyl, allyl, $\beta(\beta'$-ethoxy)-ethoxyethyl, benzyl or a furfuryl group; the substituent Y is a hydrogen atom or a phenyl, chlorophenyl, methoxyphenyl, ethoxyphenyl, tolyl, cyclohexyl or a pyridyl group; and the substituents R_1 and R_2 (which may be the same or different) are hydrogen atoms or chlorine, fluorine or bromine atoms or methyl, ethyl, propyl, butyl, trifluoromethyl, methoxy, ethoxy, methylthio, ethylthio, methanesulphonyl or ethanesulphonyl groups.



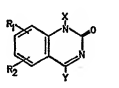
where m', m'', m''' are 0, 1 or 2 and m is 1 or 2).

12. 4 - Aryl - quinazolinones of general formula:



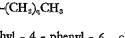
WHAT WE CLAIM IS:—

1. Quinazolinones of the general formula



I

(in which X is a substituted or unsubstituted alkyl group containing 1 to 6 carbon atoms, alkenyl group, or aralkyl group; the group $-CH_2Z$, wherein Z is a substituted or unsubstituted heterocyclic group or; the group



3. 1 - methyl - 4 - phenyl - 6 - chloro - 2-[1 *H*]-quinazolinone.

4. 1 - methyl - 4 - ortho - tolyl - 6-chloro-2-[1 *H*]-quinazolinone.

5. 1 - methyl - 4 - phenyl - 6 - methoxy-2-[1 *H*]-quinazolinone.

6. 1 - methyl - 4 - phenyl - 7 - chloro-2-[1 *H*]-quinazolinone.

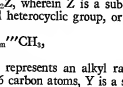
7. 1 - ethyl - 4 - phenyl - 6 - chloro-2-[1 *H*]-quinazolinone.

8. 1 - methyl - 4 - para - chloro - phenyl-6-chloro-2-[1 *H*]-quinazolinone.

9. 1 - methyl - 4 - meta - chloro - phenyl-6-methoxy-2-[1 *H*]-quinazolinone.

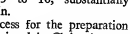
10. 1 - ethyl - 4 - ortho - tolyl - 6-chloro-2-[1 *H*]-quinazolinone.

11. Compounds of the formula



I

(in which R_1, R_2 and Y are as defined in Claim 1 and X is a substituted or unsubstituted alkyl group containing 1 to 6 carbon atoms, alkenyl group or aralkyl group, or the group $-CH_2Z$, wherein Z is a substituted or unsubstituted heterocyclic group, or the group

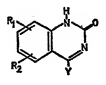


(in which X represents an alkyl radical containing 1 to 6 carbon atoms, Y is a substituted or unsubstituted phenyl radical and R is a halogen atom or an alkoxy radical in the 6- or 7-position).

13. Compounds as claimed in Claim 1, with the exception of those claimed in any of Claims 3 to 10, substantially as described herein.

14. A process for the preparation of compounds as claimed in Claim 1 comprising re-

action of a quinazolinone of the general formula



II

(in which R_1, R_2 and Y are as defined above for formula I) with a basic agent followed by reaction with a compound of the general formula

X—Q or X′—Q

(in which X is as defined for formula I; X′ is a radical convertible in the product into a radical X as defined for formula I; and Q is a reactive ester radical) followed by subsequent conversion of the radical X′ into X where required.

15. A process as claimed in Claim 14, in which Q is a halogen atom, a sulphate group or a substituted or unsubstituted hydrocarbon sulphonate group.

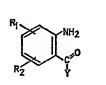
16. A process as claimed in Claim 14, in which the basic agent which is reacted with the quinazolinone of formula II is an alkali metal hydride, sodamide, sodium ethoxide or sodium hydroxide.

17. A process as claimed in Claim 16 in which the basic agent is sodium hydride.

18. A process as claimed in Claim 16 in which the quinazolinone of formula II is reacted with an akali metal hydride in dimethylformamide at room temperature.

19. A process as claimed in Claim 14 in which the reaction of X—Q or X′—Q with the quinozolinone salt is effected at room temperature.

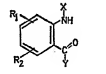
20. A process as claimed in any of Claims 14 to 19 in which the compound of the formula II, as defined in Claim 14, is prepared by the condensation at an elevated temperature of an amino aldehyde or amino ketone of general formula



III

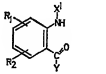
(in which R_1, R_2 and Y are as defined for formula I) with a reagent containing an N—C—O linkage, selected from the group consisting of urea, cyanic acid, a carbamate and carbamyl chloride.

21. A process for the preparation of compounds of the formula I, as claimed in Claim 1, comprising condensation at an elevated temperature of an aminoaldehyde or aminoketone of the general formula



IV

or



IVa

(in which R_1, R_2, Y and X are as defined in Claim 1 and X′ is a radical convertible into the radical X) with a reagent containing the linkage N—C—O, selected from urea, cyanic acid, a carbamate and carbamyl chloride, followed by subsequent conversion of the radical X′ into X where required.

22. A process as claimed in Claim 20 or Claim 21 in which cyanic acid is formed *in situ* by using an alkali metal cyanate and operating in an acid medium at a temperature of from 50° C to 60° C.

23. A process as claimed in Claim 22 in which the alkali metal cyanate is potassium cyanate.

24. A process as claimed in Claim 20 or Claim 21 in which condensation with urea is effected by admixture with urea and heating.

25. A process as claimed in Claim 20 or Claim 21 in which condensation with urea is effected at a temperature of about 200° C.

26. A process for the preparation of compounds as claimed in Claim 1 substantially as described herein.

27. A Process as claimed in any of Claims 14, 20 and 21 substantially as described herein with reference to any of Examples I to IX, Table A or Table B.

28. Compounds as claimed in Claim 1 whenever prepared by a process as claimed in any of Claims 14, 20 or 21.

29. Pharmaceutical compositions comprising as active ingredient at least one compound as claimed in Claim 1 in association with a pharmaceutical carrier or excipient.

30. Compositions as claimed in Claim 29 prescribed in a form suitable for oral, rectal topical or parenteral administration.

31. Compositions as claimed in Claim 30 in the form of granules, tablets, coated tablets, capsules, syrups, emulsions, suspen-

sions, drops, suppositories, ointments, creams, lotions or topically-applied sprays or aerosols.

32. Compositions as claimed in Claim 29 in the form of dosage units.

33. Compositions as claimed in Claim 32 in which each dosage unit contains 50 mg to 1.0 g of active ingredient.

34. Composition as claimed in Claim 33 in which each dosage unit contains 100 mg to 0.5 g of active ingredient.

35. Compositions as claimed in Claim 32 in the form of tablets, coated tablets, capsules, suppositories or ampoules.

36. Compositions as claimed in Claim 29 substantially as described herein.

For the Applicants,
FRANK B. DEHN & CO.,
Imperial House, 15—19, Kingsway,
London, W.C.2.

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